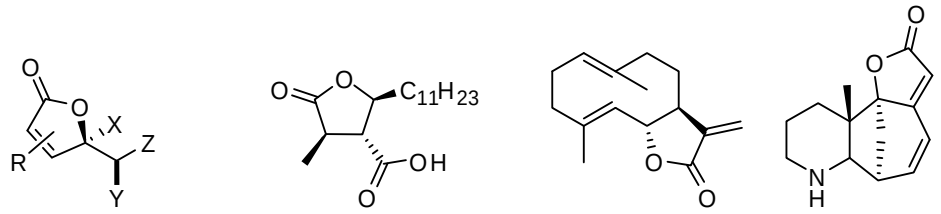
Chapter 6

Combining asymmetric allylic alkylation and ring closing metathesis: an avenue to biologically active compounds

6.1 Introduction

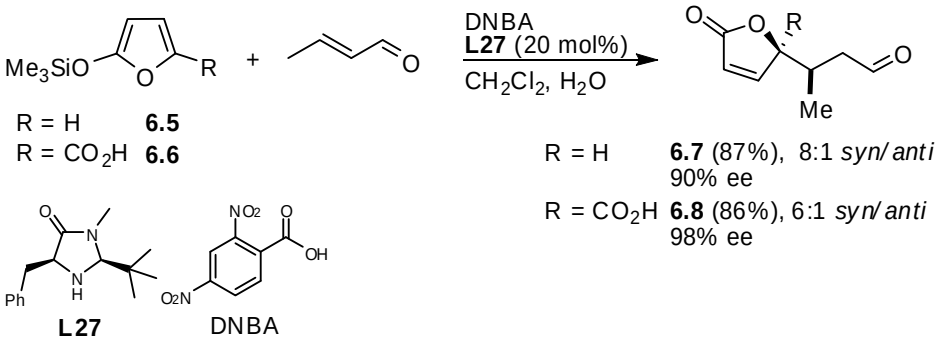
The γ-butenolide subunit **6.1** is present in more then 13000 natural products (Figure 1).[1] A wide variety of naturally occurring mono-, di and trisubstituted butyrolactones **6.2** are known as well as more complex architectures such as bi-cyclic and tri-cyclic ring systems (**6.3** and **6.4**, respectively). Butyrolactones encompass a broad range of biological activities including antibiotic, anti tumour[2], antiviral HIV-1[3], anti inflammatory[4] and antifungal activity.[5] Besides pharmaceutical applications γ-butyrolactones have been used as selective catalysts[6] and chiral dopants for ferroelectric liquid crystals. [7]



6.1 γ-Butenolides **6.2** Nephrosteranic acid **6.3** Costunolide **6.4** Securine

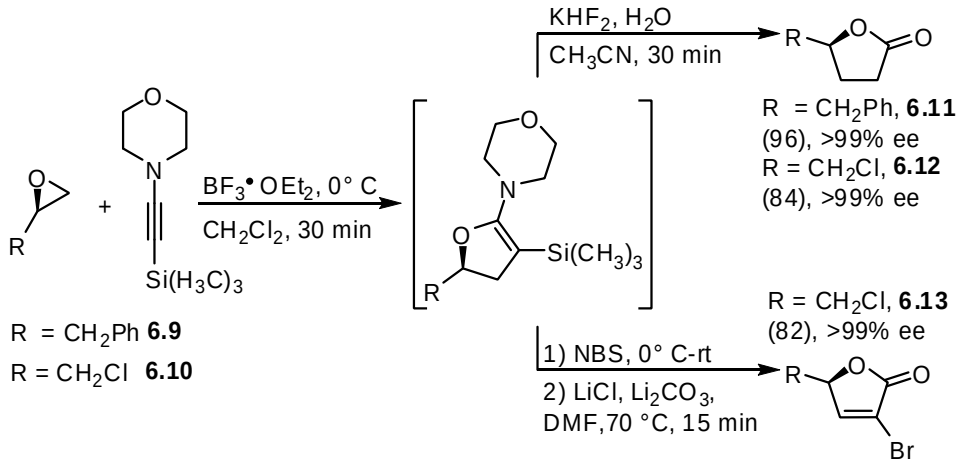
Figure 1: *γ-Butyrolactones, bi- and tricyclic ring systems*

Developing new asymmetric methods to access these valuable compounds has therefore received ample interest during the past decades.[8] In this context numerous strategies have been reported[9]. Iminium organocatalysis with imidazolidinone catalyst **L27** developed by MacMillan and coworkers[1] is one of the most versatile and powerful methods to obtain enantiomerically enriched γ-butenolides (Scheme 1, **6.7** and **6.8**). α,β-Unsaturated iminium ions arising from catalyst **L27** and unsaturated aldehyde, undergo 1,4-addition of the π-nucleophile, e.g. siloxy furan **6.5** or **6.6**, in a highly selective manner. The observed unusual chemo- and *syn* stereoselectivity can be attributed to steric constraints imposed by the catalyst structure.



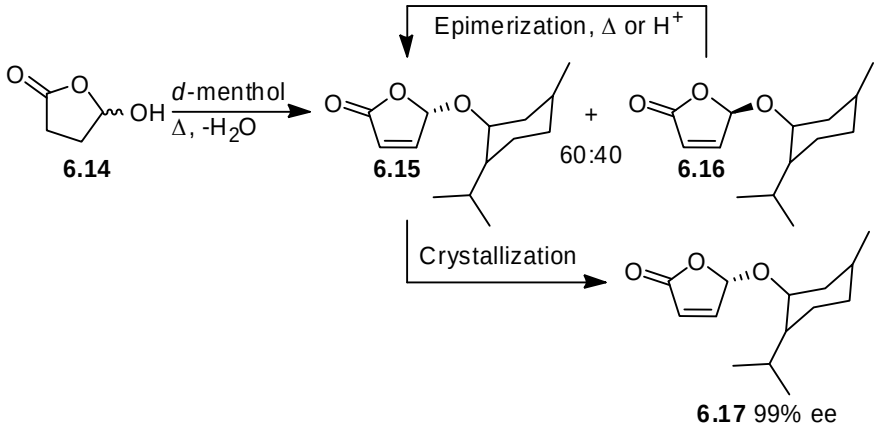
Scheme 1: γ-*Butenolide synthesis via the Mukaiyama-Michael reaction.*

Jacobsen *et al* developed a route toward the synthesis of enantiomerically enriched γ-butyrolactones (Scheme 3).[10] Elaborating on his kinetic resolution protocol of epoxides via catalytic hydrolysis with chiral cobalt-based salen complexes,[11] enantiopure epoxides e.g. **6.9** and **6.10** were by treated with an ynamine in the presence of $BF_3 \bullet OEt_2$ (Scheme 2). After hydrolysis of the cyclic keteneaminal intermediate γ-butyrolactones **6.11** and **6.12** were obtained in high yield and enantioselectivity. γ-Butenolides **6.13** could be accessed via brominating the cyclic keteneaminal with *N*-bromosuccinamide (NBS) followed by elimination with $LiCl/Li_2CO_3$.



Scheme 2: *γ-Butyrolactone synthesis via ring opening of epoxides.*

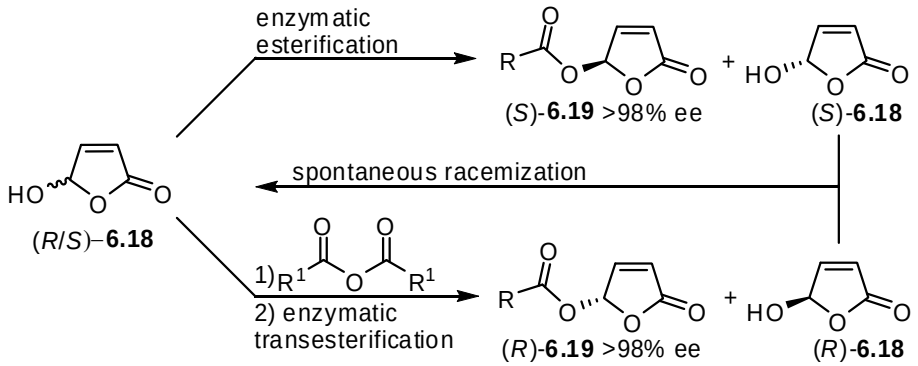
Our group has been involved in this particular field of research for over two decades also. Two practical synthesis routes toward enantiomerically enriched γ-butenolides were developed (Scheme 3), classic resolution of 5-hydroxy-2(*5H*) furanone **6.14** with *d*-menthol, provides after crystallization diastereomerically pure product **6.17.**



Scheme 3: *γ-Butenolide synthesis via classic resolution.*

An important feature of this method is that the menthol adducts are susceptible to epimerization of the acetal centre when heated or subjected to acidic conditions. Epimerization of the mother liquor furnishes a 60:40 mixture of diastereoisomers again. In this fashion, yields of 70% were obtained for this second order asymmetric transformation. The opposite configuration can be accessed by the use of *l*-menthol.[12]

The second method, stereoselective acylation of 5-hydroxy-2(*5H*) furanone **6.18** with vinyl acetate through a lipase catalysed dynamic kinetic resolution (DKR), allows complete conversion of racemic **6.18** to enantiopure **6.19** (scheme 4).[13] Both enantiomers can be obtained using this DKR protocol.



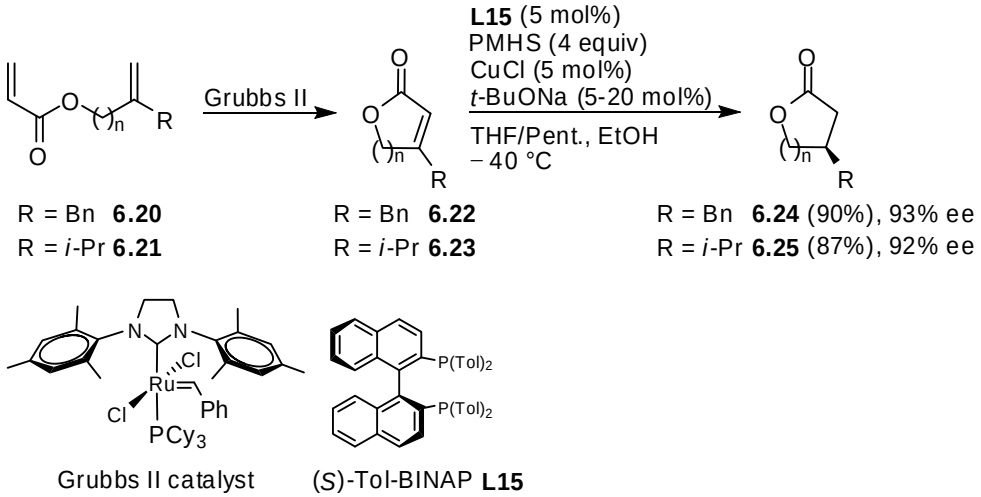
Scheme 4: *γ-Butenolide synthesis via lipase mediated dynamic kinetic resolution.*

For instance, acylation of 5-hydroxy-2(*5H*) furanone(*R,S*)-**6.18** gives (*S*)-5-acetoxy-2(*5H*)-furanone **6.19** (R = Me). Esterification with a suitable anhydride followed by lipase catalysed transesterification of racemic 5-acetoxy-2(*5H*)-furanone **6.18** provides (*R*)-5-acetoxy-2(*5H*)-furanone **6.19**.

However, a fully transition-metal catalysed asymmetric synthesis route toward the γ–butenolide subunit has not been reported so far to the best of our knowledge. Such a route would be highly desirable since it avoids the use of stoichiometric reagents and the limitations often imposed by enzymes. In this chapter a versatile and practical catalytic asymmetric synthesis route toward γ–butenolides based on the *h*-AAA reaction (Chapter 5) followed by ring closing metathesis (RCM) is being described.

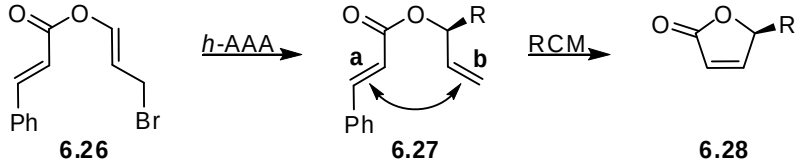
6.2 Synthesis strategy: toward γ-butenolides based on *h*-AAA reactions followed by ring closing metathesis

Besides the wide variety of synthetic methods that have been developed to access the γ-butenolide subunit[8] Buchwald *et al* reported the facile enantioselective synthesis of closely related β-substituted butyrolactone e.g. **6.24** and **6.25** based upon ring closing metathesis (RCM)[14] of dienes **6.20** and **6.21** followed by catalytic enantioselective reductive conjugate addition using CuCl/**L15** and polymethylhydrosiloxane, PMHS (Scheme 5).[15]



Scheme 5: *β-Substituted butyrolactone synthesis via RCM followed by reductive 1,4-addition.*

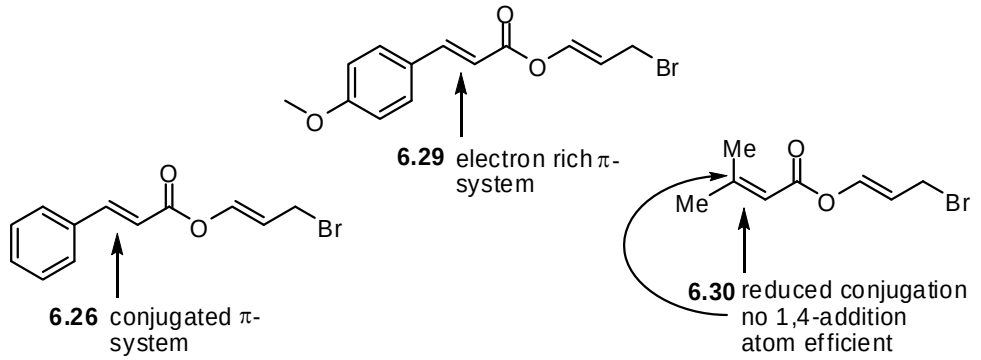
This research combined with the tandem consecutive AAA-RCM reaction developed by Alexakis *et al* (see Chapter 1, § 1.3.9) and the realization of the *h*-AAA reaction (Chapter 5) inspired us to a new short 2 step catalysed asymmetric synthesis route toward enantiomerically enriched γ-butenolides **6.28**. Furthermore this reaction sequence transforms the cinnamate ester from a 'redundant' protecting group into a functional group. Thus, *h*-AAA of allylic bromide **6.26** (R = linear aliphatics) gives enantiomerically enriched allylic ester **6.27**. RCM of the terminal olefin **b** created during the *h*-AAA reaction and the cinnamate ester moiety **a** as a metathesis partner completes the synthesis of γ-butenolide **6.28**.



Scheme 6: *γ–Butenolide synthesis via h-AAA followed by RCM.*

6.3 Substrate reactivity and synthesis

Cinnamate derived substrate **6.26** has already been used with success in the *h-AAA* reaction (Chapter 5, § 5.4.3). Although RCM of compounds such as **6.26** may seem trivial, the electron delocalization of the α-β unsaturated π-system into the aromatic ring leading toward an extended conjugated π–system may cause a diminished reactivity of the α-β unsaturated π-system toward the RCM reaction.



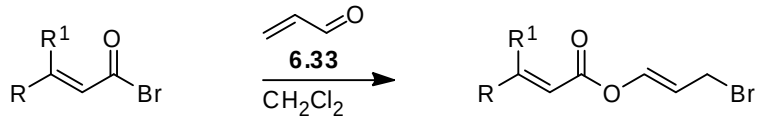
Scheme 7: *Substrates for h-AAA followed by RCM.*

The use of the olefin of cinnamate esters as a metathesis partner has, to the best of our knowledge, not been reported so far. Although numerous RCM synthesis toward heterocycles are reported, the metathesis partners all belong to the group of terminal unsubstituted alkenes or substituted alkenes that are not part of a highly conjugated π-system such as cinnamate esters.[16]

The influence of increased electron density on the conjugated internal olefin of the cinnamate group toward RCM can be assessed by introduction of an electron donating group, like the MeO-group **6.29**, at the *para* position on the phenyl ring. However, in light of the current environmental awareness[17], the atom efficiency[18] of such cinnamyl derivatives is surely not ideal since the following RCM renders the phenyl group superfluous. Therefore a more atom-economical substrate, such as **6.30**, bearing two methyl groups on the β-position was investigated also. Furthermore, the π-system of the internal olefin of **6.30** is relatively electron rich since it is no longer in conjugation with any neighbouring aromatic group. Moreover, the β-carbon of **6.30** is a tertiary carbon and therefore not susceptible to 1,4-addition with the catalyst used for the *h*-AAA reaction.

6.3.1 Substrate synthesis

Compounds **6.26, 6.28** and **6.29** were synthesized according to, or by minor modification of, the procedure previously described in (Chapter 5, for compound **6.26** see § 5.3).



R = *p*-MeOC$_6$H$_4$, R^1 = H **6.31** — R = *p*-MeOC$_6$H$_4$, R^1 = H **6.29** (47%)

R = Me, R^1 = Me **6.32** — R = Me, R^1 = Me **6.30** (27%)

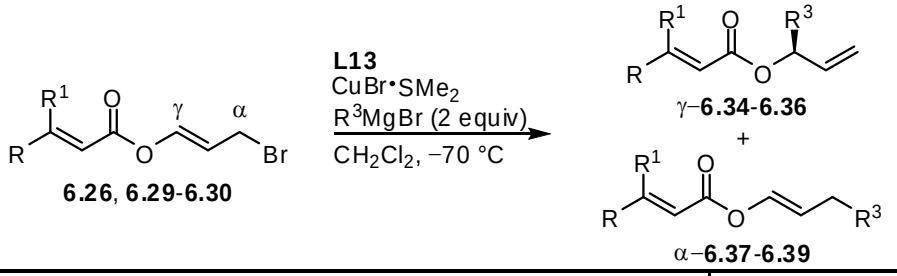
Scheme 8: *Synthesis of allylic bromides.*

Reaction of acrolein **6.33** with the bromides **6.31** and **6.32,** obtained via bromination of the corresponding acid with PPh_3/Br_2 in CH_2Cl_2, afforded after crystallisation from *n*-pentane pure *E*-products **6.29** and **6.30** as white crystalline needles in moderate yield (Scheme 8). In general these types of allylic bromides can be crystallised at –15 °C from *n*-pentane/ethyl acetate mixtures or pure *n*-pentane, however **6.30** did not crystallise from pure *n*-pentane at –15 °C, but had to be crystallized from *n*-pentane at –50 °C instead. In addition **6.30** proved to be difficult to handle due to its instability: slow decomposition at room temperature, and sensitivity to atmospheric conditions (most likely hydrolysis).

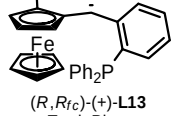
6.4 *h*-AAA followed by RCM on cinnamic and aliphatic 3-bromopropenyl esters

When **6.30** was subjected to optimized *h*-AAA conditions, using 1 mol% catalyst, **6.34** was obtained in moderate yield (**6.34**, is a volatile compound) and good regioselectivity (Table 1, 66 %, 95:5, entry 1). Substrate **6.29** bearing an electron donating group *para* on the benzyl ring underwent *h*-AAA with BuMgBr providing product **6.35** in moderate yield and excellent regioselectivity (entry 2).

Table 1: *h-AAA reactions of different substrates.*



entry(product)	R	R^1	R^3	yield (%)	γ:α[a]	ee (%)[b]
1 (**6.34**)	Me	Me	Et	66	95:5	--
2 (**6.35**)	*p*-MeOC$_6$H$_4$	H	Bu	70	>95:5	--
3 (**6.36**)[c]	Ph	H	Et	80	>95:5	98



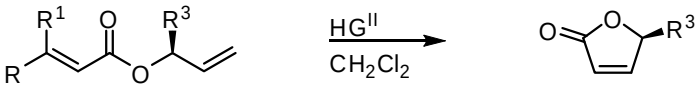
(*R*,*R*$_{fc}$)-(+)-**L13**
TaniaPhos

[*] Reaction conditions: CuBr•SMe$_2$ 1 mol%, **L13** 1 mol%, 2 equiv Grignard reagent, t = ~20 h, unless noted otherwise. [a] Determined by ^{1}H NMR spectroscopy. [b] Ee determined by HPLC chromatography over a chiral stationary phase after conversion to known butyrolactone **6.40**. [c] CuBr•SMe$_2$ 0.5 mol%, **L13** 0.5 mol%.

Interestingly, the rate of the reaction was slightly lower, 3 d vs. typically 20 h to reach full conversion. We then submitted the standard cinnamyl-derived substrate **6.26** to *h*-AAA reaction conditions. Conversion of **6.26** to the desired γ-product **6.36** was achieved using CuBr/**L4** (0.5 mol%) and EtMgBr (2 equiv) in good yield, excellent regio- and enantioselectivity using only 0.5 mol% catalyst (80%, 98% ee, entry 3). This result demonstrates that substrate **6.26** is the best substrate so far for the synthesis of chiral γ-butenolide precursors.

Next we decided to test the RCM reaction on the three sterically and electronically different substrates synthesized (*vide infra)*. When **6.34** was submitted to RCM conditions using Hoveyda Grubbs^{2nd} generation catalyst (HG^{II}) in CH_2Cl_2 no formation of the ring closed product was observed (thin layer chromatography, TLC, analysis) during 24 h. After addition of an extra portion of catalyst (5 mol%) and 4 d of reflux, ^{1}H NMR spectroscopic analysis of the crude mixture showed complete conversion of **6.34** to predominantly the desired product **6.40** and a trace amount of dimer-**6.34** and by-products (Table 2, entry 1).[19] However, the availability of substrate **6.34** is greatly impaired by its thermal instability, air sensitivity and difficult purification. The RCM of *p*-MeO substituted substrate **6.35** was investigated using HG^{II} catalyst. The formation of the desired product was observed, alongside with *p*-MeO-stilbene by-product **6.41** (^{1}H NMR spectroscopic analysis).[20] The moderate yield was attributed to arduous purification procedures to remove the *p*-MeO-stilbene by-product **6.42** via multiple crystallisations and sequential (2x) column chromatography (entry 2, 41%).

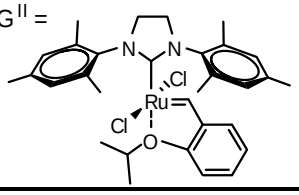
Table 2: *RCM of compounds **6.40** and **6.41** using HG^{II} catalyst.*

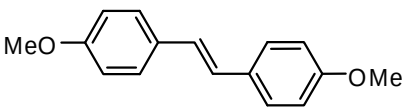


6.34-6.36 **6.40-6.41**

entry(product)	R	R^1	R^3	HG^{II}(mol%)	T(°C)	t(days)	Convn(%)[a]	ee(%)[b]
1[c] (**6.40**)	Me	Me	Et	2 x 5	reflux	4	100	nd
2[d] (**6.41**)	*p*-$MeOC_6H_4$	H	Bu	3 x 1	rt/reflux	12	100 (41)	nd
3[e] (**6.40**)	Ph	H	Et	10	reflux	2	100 (78)	98

HG^{II} =





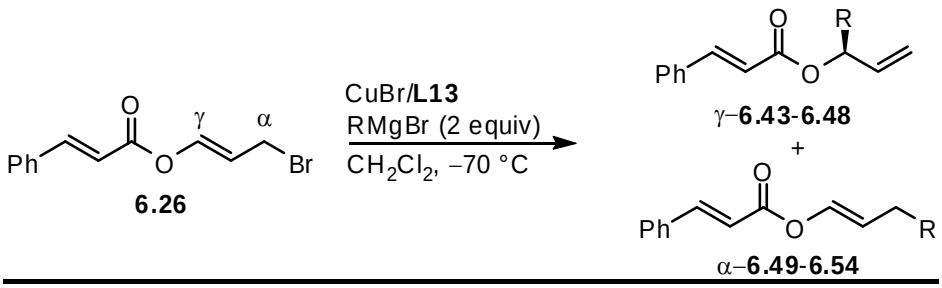
6.42

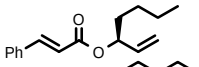
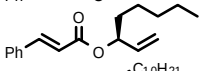
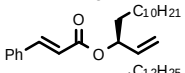
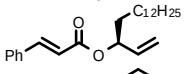
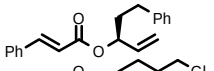
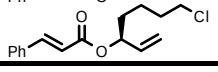
* [a] Conversion determined by ^{1}H NMR spectroscopy; isolated yield reported in parenthesis. [b] ee determined by HPLC chromatography over a chiral stationary phase. [c] Reaction conditions: 5 mol% HG^{II}, 50 ml CH_2Cl_2, reflux 24 h; Concentrate to 5 ml, add 5 mol% HG^{II}, reflux. 3 d. [d] Reaction conditions: 3 x 1 mol% HG^{II}, 10 ml CH_2Cl_2, rt, 9 d, reflux 3 d. [e] 5.0 mM solution, nd = not determined.

Moreover the rate of the reaction was substantially lower, leading to inconvenient reactions times of 12 d. Finally we tested cinnamate substrate **6.36**. Treating **6.36** (5.0 mM solution in CH_2Cl_2) with HG^{II} (10 mol%) after 2 d of heating to reflux, γ-butenolide **6.40** was obtained in good yield and with retention of enantiomeric excess.

The above results show that the standard cinnamyl substrate **6.26** outperforms substrates **6.29** and **6.30** in the *h*-AAA and in the RCM reaction. We therefore decided to use substrate **6.26** as the starting material for the addition of a variety of Grignard reagents using the *h*-AAA-RCM protocol to synthesize a number of γ-butenolides. Substitution of substrate **6.26** with a number of linear Grignard reagents proceeded with high yields and regio- and enantioselectivity (Table 3, entries 1 to 4).

Table 3: *h-AAA reactions of substrate* ***6.26*** *with various Grignard reagents.*



entry	(product)	R		yield(%)	γ:α[a]	ee(%)[b]
1	(**6.43**)	*n*-Bu		92	>95:5	>98(*S*)
2	(**6.44**)	*n*-Pentyl		84	>95:5	>98(*S*)
3	(**6.45**)	$C_{11}H_{23}$		73	>95:5	>98(*S*)
4[c]	(**6.46**)	$C_{13}H_{27}$		68	>95:5	nd
5	(**6.47**)	C_2H_4Ph		–	–	–
6[d]	(**6.48**)	C_4H_8Cl		<5[e]	nd	nd

[*] Reaction conditions: 5 mol% CuBr•SMe_2, 5 mol% **L13**, 2 equiv Grignard reagent, t = ~20 h, unless noted otherwise, nd = not determined. [a] Determined by ^{1}H NMR spectroscopy. [b] Determined by comparison of optical rotation reported in literature after conversion to known γ-butenolides, see exp. section, [c] T = –55 °C. [d] t = 45 min. [e] Conversion, determined by ^{1}H NMR spectroscopy.

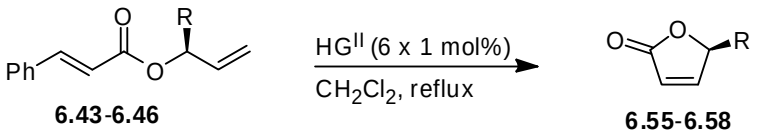
Substitution with long alkyl chain Grignard reagents was performed at higher temperatures to prevent precipitation of the Grignard reagent from the reaction mixture at low temperatures (–55 °C, entry 7). The regio- and enantioselectivity of the reaction was not influenced by elevated temperatures, this in accordance with observations made when using benzyloxy ester substrates (Chapter 5). However, a

decrease in yield was observed when using longer alkyl Grignard reagents (entry 1-4, 92-68%). Substitution with functionalized Grignard reagent PhC_2H_4MgBr did not afford the desired branched product **6.48**. ^1H NMR spectroscopic analysis of the crude mixture showed a complex mixture of by-products and a trace amount of the derived product. 'Aging' of the Grignard reagent could have been the cause of failure. However, reaction with freshly prepared PhC_2H_4MgBr (3 M, Et_2O) gave similar results (entry 5). Substitution with chloride functionalized Grignard reagent provided a complex reaction mixture of predominantly by-products and a trace amount of the desired product **6.48**. The rate of substrate consumption was considerably faster though (entry 6, 45 min, TLC analysis). In contrast with benzyloxy ester substrates that can be substituted with functionalized Grignard reagents (chapter 5), cinnamyl derived substrates are less versatile substrates.

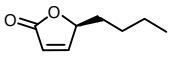
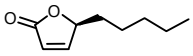
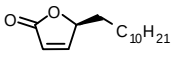
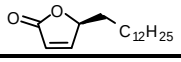
6.5 Ring closing metathesis of *h*-AAA products

When compound **6.43** was treated with HG^{II} in CH_2Cl_2 (5.0 mM) at reflux for 7 d, the desired ring closed product **6.55** was obtained in good yield (Table 4, entry 1, 74%). Likewise were compounds **6.44-6.46** subjected to RCM conditions and converted to the corresponding γ-butenolides **6.56-6.58** in good yields and with retention of enantioselectivity (entries 2-4). A relation could be drawn between the rate of the RCM reaction and the length of the aliphatic alkyl chain R.[21] The longer the alkyl chain R, the lower the reaction rate: C_2/2 d; C_4/7d; C_{11}/14 d. Moreover, the yield of the RCM reaction decreased with the increasing reaction times and chain length. (Table 4, entries 1-4).

Table 4: *RCM of h-AAA reaction products.*

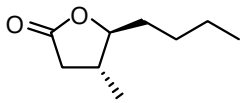


6.43-6.46 → **6.55-6.58**

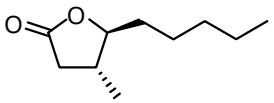
entry(product)	R		t(d)	yield(%)	ee(%)[a]
1 (**6.55**)	*n*-Bu		7	74	>98(*S*)
2 (**6.56**)	*n*-Pentyl		7	72	>98(*S*)
3 (**6.57**)	$C_{11}H_{23}$		14	71	>98(*S*)
4 (**6.58**)	$C_{13}H_{27}$		14	67	nd

[a] Determined by comparison of optical rotation reported in literature, see exp. section, nd = not determined.

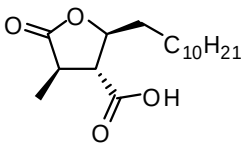
To illustrate the synthetic potential of the *h*-AAA-RCM protocol, synthesized γ-butenolides **6.55-6.58** were used as building blocks for the synthesis of four biologically relevant molecules. The molecules of interest are: whiskey lactone [22], cognac lactone[23], nephrosteranic[24] and roccerellic acid.[25] (Figure 2)



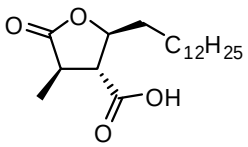
(−)-whiskey lactone **6.59**



(−)-cognac lactone **6.60**



(−)-nephrosteranic acid **6.61**

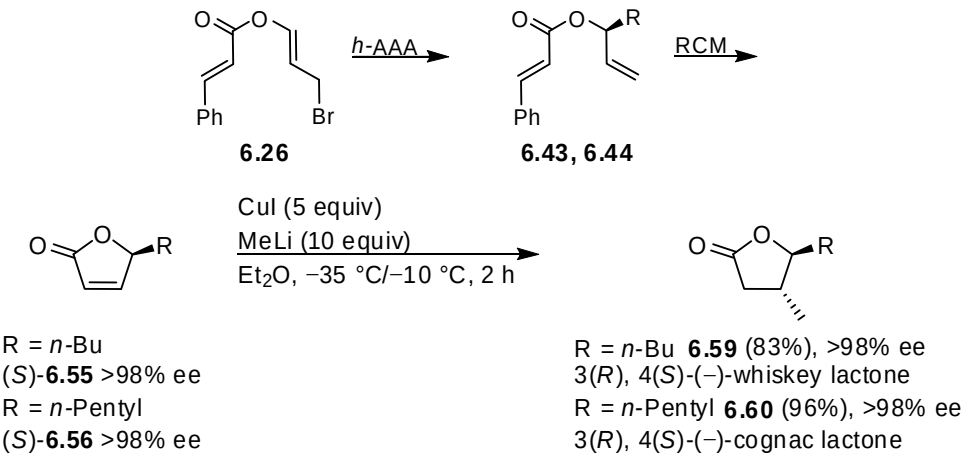


(−)-roccellaric acid **6.62**

Figure 2: *Target molecules.*

6.6 Synthesis of whisky and cognac lactones and the total synthesis of nephrosteranic acid and roccellaric acid

Whiskey **6.59** and cognac **6.60** lactones are among the most well known flavour and perfume compounds. These lactones are also referred to as quercus lactones. Quercus lactones originate from quercus (oak) trees, although quercus lactones are also present in other types of trees and plants. Quercus lactones are responsible for the sensory characteristics of wine and other alcoholic beverages[26] such as whisky, brandy and cognac, in which they are extracted during their ageing in oak barrels. All of the four possible stereoisomers of whisky and cognac lactones have their own distinct taste and aroma[27] and are extensively used in the perfume and flavour industry. Not surprisingly, numerous syntheses of racemic and scalemic whisky[28] and cognac lactones[29] can be found in the literature. Our proposed synthesis strategy (Scheme 9) is based on the use of transition-metal catalysed transformations only.

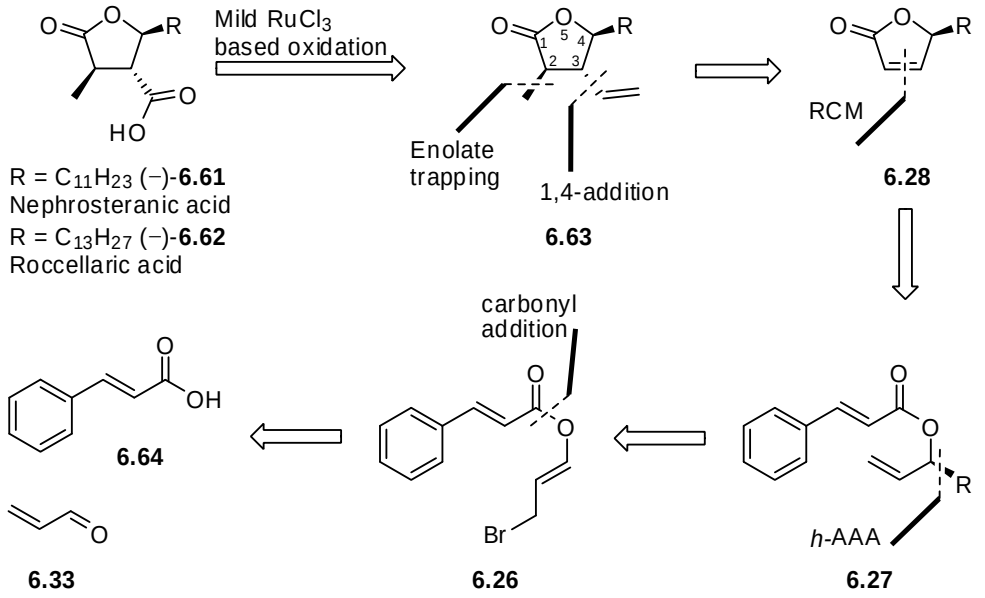


Scheme 9: *Synthesis of whiskey and cognac lactones **6.59** and **6.60**.*

With the requisite chiral butenolides **6.55** and **6.56** in hand (obtained via the *h*-AAA-RCM route, *vide supra*), we carried out the synthesis of whisky and cognac lactones **6.59** and **6.60.** Chiral γ-butenolides have been shown to be good Michael acceptors.[30] The conjugate addition of Gilman reagent,[31] dimethylcopper lithium to **6.55** provided (–)-**6.59** in 83% yield with excellent diastereoselectivity and complete preservation of enantioselectivity. As expected, the alkyl substituent at the γ-position in **6.55** directs the introducing methyl moiety to an *anti*-attack with respect to the γ-substituent. Analogously, **6.56** was converted into *trans*-(–)-**6.60** in 96% yield. Spectroscopic data of **6.59** and **6.60** were corresponding to those reported in literature (see experimental section).[28e,f]

6.6.1 Total synthesis of (–)-nephrosteranic acid and (–)-roccellaric acid

The two furanones, (+)-nephrosteranic acid **6.61**, (+)-roccellaric acid **6.62** have been isolated from lichens: nephromopsis endocrocealoa[24] and roccellaria mollis,[25] respectively. The first asymmetric synthesis of nephrosteranic acid **6.61**, was reported by Momose *et al* in 1995,[28e,f] whereas roccellaric acid **6.62** was synthesized in optically pure form by Mulzer *et al*. two years prior to the synthesis of nephrosteranic acid[32]. Although numerous synthetic strategies toward **6.61** and **6.62** have been reported since the syntheses of Mulzer and Momose, [33] we present here a synthesis strategy based on reliable cuprate chemistry and ring closing metathesis technology. The complete synthesis strategy is outlined in a retrosynthetic fashion in Scheme 10.

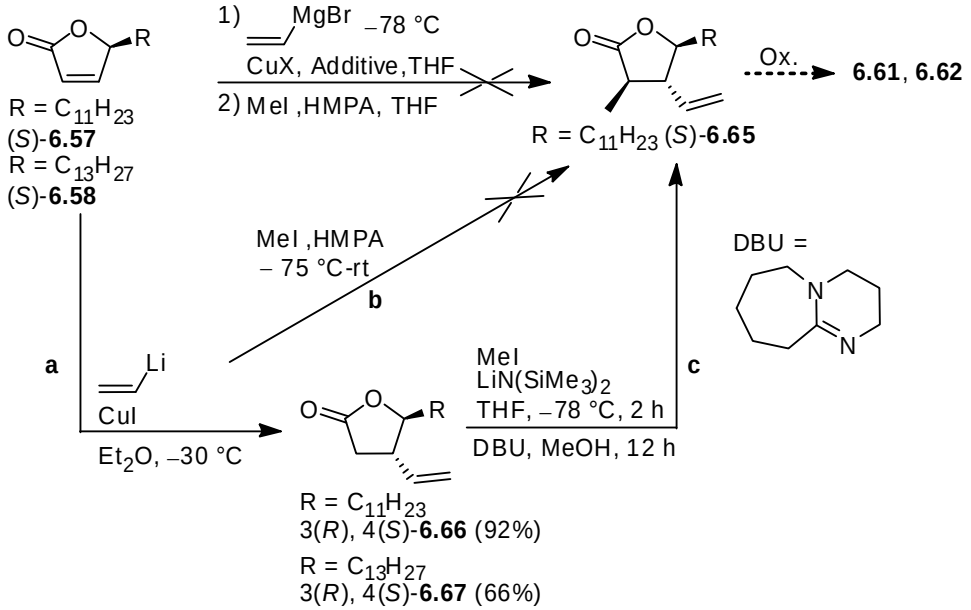


Scheme 10: *Retrosynthesis of (–)-nephrosteranic acid* ***6.61*** *and (–)-roccelaric acid* ***6.62***.

Trisubstituted lactone **6.63** presents itself as a key synthetic intermediate; it was projected that the asymmetric synthesis of nephrosteranic and roccellaric acid could be achieved in the event that the olefinic moiety in **6.63** could be oxidized toward the acid without epimerization. One way of introducing the 2,3-substitution pattern of intermediate lactone **6.63** is by means of a cuprate-mediated conjugate addition of Grignard or lithium reagents to γ-butenolide **6.28** followed by trapping of the intermediate enolate with the appropriate alkylating agent. The stereochemistry of the conjugate addition and subsequent enolate trapping is anticipated to occur in a double *anti* fashion due to the expected directing influence of the alkyl substituent at the γ-position, analogous to the synthesis of whiskey and cognac lactones **6.59** and **6.60**. Thus intermediate **6.63** can be traced to butenolide **6.28**, of which the synthesis via the *h*-AAA-RCM protocol, has been discussed in

detail earlier (*vide supra*). Overall a total synthesis strategy of **6.61** and **6.62** was outlined to encompass 5 steps starting from the cheap commercially available bulk chemicals cinnamic acid **6.64** and acrolein **6.33**.

The reduction of the synthesis strategy to practise is addressed in Scheme 11. Our initial attempts to obtain key intermediate **6.63** were based on a tandem consecutive 1,4-addition enolate alkylation starting from γ-butenolides **6.57** and **6.58**. Thus using a slight modification of the method reported by Hanessian *et al*:[34] i.e. $CuBr{\bullet}SMe_2$ in place of CuI and omission of Me_2S, **6.57** was reacted (at –40 °C) with a solution of vinylMgBr (1.1 equiv., 1 M sol. THF) and CuX = $CuBr{\bullet}SMe_2$ (1.1 equiv.) at –78 °C using THF as the solvent (Scheme 11). Hexamethylphosphoric acid (HMPA, 10 equiv.) and methyl iodide (10 equiv.) were added after 1 h stirring and the reaction mixture was allowed to warm to room temperature before stirring for 2 d. ^{1}H NMR spectroscopic analysis, after quenching, of the crude reaction mixture showed unreacted starting material exclusively. Surprisingly the conjugate addition had not taken place. To investigate the reactivity of butenolide **6.57** toward conjugate addition with Grignard reagents, the 1,4-addition was repeated using the same ratios of reagents, but the reaction mixture was allowed to warm to –20 °C. No reaction occurred according to TLC analysis.



Scheme 11: *Synthesis of (–)-nephrosteranic acid* ***6.62*** *and (–)-roccellaric acid* ***6.63***.

Subsequently an extra two equivalents of vinylMgBr were added at –40 °C and the reaction was allowed to gradually warm to room temperature. TLC analysis showed the formation of a number of products with incomplete conversion of starting material after 1 h. Prolonged reaction times, 2 d at room temperature and

addition of another 2 equivalents of Grignard reagent resulted in full consumption of starting material to predominantly by-products and possibly product (^{1}H NMR spectroscopic analysis). Following the procedure of Danishefsky *et al* for the 1,4-addition of vinylMgBr to bicyclic enamides[35], butenolide **6.57** was reacted at -78 °C with a cuprate reagent, prepared from vinylMgBr (3 equiv.) and X = CuI (2 equiv.) at –20 °C, in the presence of TMSCl (2 equiv.) for 2 h. Remarkably, ^{1}H NMR spectroscopic analysis of the crude reaction mixture showed starting material only. It is known though that the Grignard reagents provided by Sigma Aldrich can have impurities in them that can render the Grignard reagent inactive for certain transformations. However, when vinylMgBr (0.97 M, as a sol. in THF, 3 equiv) prepared freshly was used in combination with CuI (1.5 equiv) and TMSCl (2 equiv) no reaction occurred at –78 °C, nor upon prolonged reaction times and warming to room temperature (determined by ^{1}H NMR spectroscopy). Due to the lack of reactivity of the α,β-unsaturated lactone moiety toward Grignard reagents, Lipschutz higher order cuprate $Li_2(CH_2{=}CH)_2CuCN$[36] was tested in the conjugate addition.[37] In an attempt to generate vinyllithium *in situ,* vinyl bromide was treated with *t*-BuLi (2 equiv, 1 equiv reacts with the formed *t*-BuBr) in THF at temperatures between –110/100 °C as described in literature,[38] before adding CuCN and slowly warming to room temperature. After the reaction mixture was once more cooled to –78 °C, substrate **6.57** was added and the reaction mixture was stirred for 1 h. However, this approach yielded unreacted starting material only, probably due to unsuccessful generation of the vinyllithium reagent. Multiple attempts to generate the vinyl lithium reagent proved it crucial to keep the temperature between –120/–115 °C to reliably obtain the vinyllithium reagent as a 0.56 M solution in Et_2O/*n*-pentane; determined via titration with diphenylacetic acid (DPAA).[39] Fortunately, reaction of butenolide **6.57** (10 equiv, 0.48 M, as a sol. in Et_2O) with freshly prepared vinyllithium, in the presence of CuI (5 equiv.) in Et_2O at –30 °C for 30 min provided the desired 1,4-addition product **6.66** in excellent yield (Scheme 9, route **a**, 92%). Analogously, **6.58** was converted into (–)-**6.67** in 66% yield. The *trans*-configuration of the substituents at position 3 and 4 were determined by comparison of ^{1}H NMR spectroscopy data of related known compounds and their characteristic chemical shift and coupling constant values for ^{1}H nuclei in a *trans*-relation.[40]

Attempts to introduce the methyl substituent at position 3 via a tandem consecutive strategy by cooling of the reaction mixture to –78 °C and subsequent addition of HMPA (10 equiv) and MeI (10 equiv) after the 1,4-addition was complete, did not result in the formation of the desired 2,3,4-trisubstituted butenolide **6.65** either (Scheme 9, route **b**). Changing the solvent system to a mixture of THF/ether (1.5:1) did not promote the formation of compound **6.65**. However, an initial reaction using $LiN(SiMe_3)_2$ (1.1 equiv) as a Brønsted base and MeI (10 equiv) in THF at –78 °C to convert **6.66** into **6.65** did provide the desired product albeit as a 1:1 mixture of two diastereoisomers (Scheme 9, route **c**). The isomers were equilibrated to the thermodynamic product with an all *anti*-stereoconfiguration, following a procedure by Hoveyda *et al,*[41] dissolving and

stirring the diastereomeric mixture of **6.66** in MeOH with an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) present at room temperature for 24 h. The total synthesis of nephrosteranic acid and roccellaric acid could, unfortunately, not be completed due to a lack of time.

6.7 Conclusions and outlook

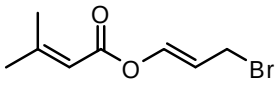
Cinnamate-derived allylic bromides proved to be the most convenient substrates for the asymmetric synthesis of chiral γ-butenolides. The substitution of cinnamate allylic bromides via a hetero allylic asymmetric alkylation gave alkylated products in high yield (up to 92%), excellent regioselectivity, >95:5 and ee's up to 98% using a number of linear Grignard reagents and the Cu/TaniaPhos complex as the catalyst. In contrast to benzoate-derived starting materials, cinnamate-derived substrates did not perform well when trying to use functionalized Grignard reagents such as $PhCH_2CH_2MgBr$ or 4-chloro-BuMgBr. HG^{II} showed to be the best catalyst to facilitate the ring closing of *h*-AAA products toward chiral butenolides without loss of ee. The ring closing of cinnamate-protected allylic alcohols followed a trend, namely that the length of the aliphatic chain of the allylic alcohol influenced the rate of the ring closing reaction. Longer chain lengths were accompanied with slower reaction rates under the conditions employed. The synthetic potential of the h-AAA-RCM protocol was illustrated with the facile synthesis of whiskey and cognac lactones. An elegant strategy toward the asymmetric synthesis of nephrosteranic acid and roccellaric acid was developed based on the *h*-AAA-RCM protocol.

Although the current limitation of the *h*-AAA-RCM protocol lies in the difficulty of introducing functionalized Grignard reagents it can be expected that, in light of the advances made by studies towards the mechanism and scope of (*hetero)*-AAA reactions, these limitations will be overcome. This event will lead toward the synthesis of highly versatile chiral butenolide building blocks in a catalytic fashion that in potential provide access to a large variety of natural products.

6.8 Experimental section

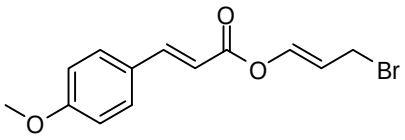
For general remarks see chapter 2.

Synthesis of starting materials[42]:



3-Methyl-but-2-enoic acid (E)-3-bromo-propenyl ester: **6. 30**.

3-Methyl-but-2-enoyl bromide **6.32** (5 g, 30.6 mmol) was added to a solution of acrolein (2.04 ml, 30.6 mmol) in CH_2Cl_2 (10 ml) at 0°C. The mixture was stirred at room temperature for 4 d before quenching with aq $NaHCO_3$ (sat). The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The organic layers were collected, dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* yielding a yellow oil. The yellow oil was taken up in *n*-pentane and **6.30** precipitated out of solution at –50 °C as thin white crystalline needles (1.8 g, 27%). **6.30** was stored under nitrogen at –15 °C: Mp.: dec. room temperature; ^{1}H NMR ($CDCl_3$, 400 MHz), δ 7.48 (td, *J* = 12.4, 1.00 Hz, 1 H), 5.71–5.62 (m, 2 H), 4.00 (dd, *J* = 8.4, 1.00 Hz, 2 H), 2.19 (d, *J* = 1.2 Hz, 3 H), 1.93 (d, *J* = 1.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 162.5 (s), 161.1 (s), 139.2 (d), 114.2 (d), 110.5 (d), 29.1 (t), 27.6 (q), 20.6 (q); MS (EI) *m/z*: 219 (M^+), 83 (100).



(E)-3-(4-Methoxy-phenyl)-acrylic acid (E)-3-bromo -propenyl ester: **6.29**.

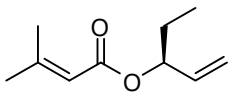
Acrolein (1.21 ml, 17.9 mmol) was added to a solution of (*E*)-3-(4-methoxy-phenyl)-acryloyl bromide **6.31** (2.95 g, 12.2 mmol) in CH_2Cl_2 (16 ml) at 0°C. The mixture was stirred at room temperature for 5 d during which a white precipitate formed. The precipitate was filtered off and the reaction mixture was partitioned between aq $NaHCO_3$ (sat) and CH_2Cl_2. The organic layer was collected, dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo* yielding a yellow oil. The yellow oil was taken up in *n*-pentane and **6.29** precipitated out of solution at –15 °C as white crystalline needles (1.7 g, 47%). **6.29** was stored at –15 °C: Mp.: dec 92 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.76 (d, *J* = 15.9 Hz, 1 H), 7.58 (td, *J* = 12.4, 1.0 Hz, 1 H), 7.52-7.48 (m, 2 H), 6.92 (m, 2 H), 6.30 (d, *J* = 15.9 Hz, 1 H), 5.78 (td, *J* = 12.4, 8.4 Hz, 1 H), 4.04 (dd, *J* = 8.4, 1.0 Hz, 2 H), 3.85 (s, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 163.7 (s), 161.9 (s), 147.0 (d), 139.4 (d), 130.1 (d, 2 x C), 126.6 (s), 114.4 (d, 2 x C), 113.3 (d), 111.0 (d), 55.4 (q), 28.9 (t), exact mass m/z calcd for $C_{13}H_{13}O_3Br$ 296.0048, found 296.0061.

***h*-AAA on α,β-unsaturated (*E*)-3-bromo-propenylesters**:

For general procedures, see chapter 5 paragraph 5.9.

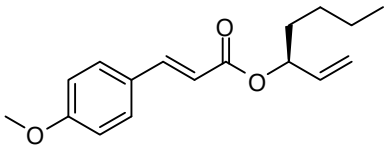
Work up procedure B:
The reaction was quenched with MeOH (5 mL). The reaction mixture was removed from the cooling bath and sat. aq. NH_4Cl (ca. 5 mL) was added. The mixture was

partitioned between CH_2Cl_2 (5 mL) and water. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*.



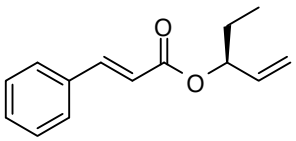
3-Methyl-but-2-enoic acid (S)-1-ethyl-allyl ester: **6.34**.

Ethylmagnesium bromide (3.0 M, 0.66 mL, 1.98 mmol) was added dropwise over 3 min to a stirred and cooled (–74 °C) solution of **6.30** (240 mg, 1.1 mmol), CuBr•SMe_2 (2.4 mg, 11 µmol) and (R,R_{fc})-TaniaPhos (7.0 mg, 10.2 µmol) in CH_2Cl_2 (3 mL) under a nitrogen atmosphere. Stirring was continued for 15 h at –74 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using Et_2O/*n*-pentane mixtures from 0-5% Et_2O, gave γ-**6.34** and α-**6.37** (122 mg, 66%, γ:α = 95:5) as a clear colorless volatile oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.76 (ddd, J = 16.9, 10.5, 6.4 Hz, 1H), 5.89-5.64 (m, 1H), 5.24-5.09 (m, 3H), 2.13 (s, 3H), 1.86 (s, 3H), 1.67-1.57 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 165.8 (s), 156.4 (s), 136.5 (d), 116.1 (t), 116.0 (d), 74.7 (d), 27.2 (t), 27.1 (q), 20.0 (q), 9.2 (q).



(E)-3-(4-Methoxy-phenyl)-acrylic acid (S)-1-vinyl-pentyl ester: **6.35**.

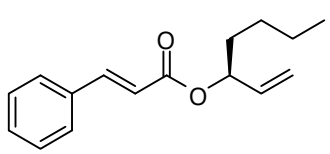
Ethylmagnesium bromide (3.0 M, 0.67 mL, 2.0 mmol) was added dropwise over 3 min to a stirred and cooled (–68 °C) solution of **6.29** (297.14 mg, 1.0 mmol), CuBr•SMe_2 (2.1 mg, 9.3 µmol) and (R,R_{fc})-TaniaPhos (6. mg, 10.0 µmol) in CH_2Cl_2 (1.5 mL) under a nitrogen atmosphere. Stirring was continued for 3 d at –68 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using Et_2O/*n*-pentane mixtures from 0-6% Et_2O, gave **6.35** (188.9 mg, 70%) as a clear colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.65 (d, J = 15.9 Hz, 1 H), 7.49-7.43 (m, 2 H), 6.92-6.85 (m, 2 H), 6.32 (d, J = 15.9 Hz, 1 H), 5.84 (ddd, J = 17.1, 10.5, 6.3 Hz, 1 H), 5.42-5.32 (m, 1 H), 5.27 (td, J = 17.2, 1.3 Hz, 1 H), 5.17 (td, J = 10.5, 1.3 Hz, 1 H), 3.80 (s, 3 H), 1.84-1.55 (m, 2 H), 1.41-1.28 (m, 4 H), 0.90 (t, J = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.4 (s), 161.2 (s), 144.2 (d), 136.7 (d), 129.5 (d, 2 x C), 127.0 (s), 116.2 (t), 115.7 (d), 114.1 (d, 2 x C), 74.4 (d), 55.1 (q), 33.9 (t), 27.1 (t), 22.3 (t), 13.8 (q); exact mass m/z calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1560.



(E)-3-Phenyl-acrylic acid (S)-1-ethyl-allyl ester: **6.36**.

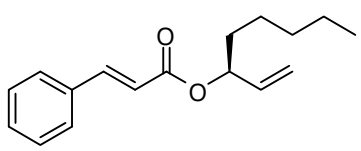
Ethylmagnesium bromide (3.0 M, 2.1 mL, 6.4 mmol) was added dropwise over 5 min to a stirred and cooled (–73 °C) solution of **6.26** (852.7 mg, 3.194 mmol), CuBr•SMe_2 (4.8 mg, 23 µmol) and (R,R_{fc})-TaniaPhos (17.2 mg, 25.0 µmol) in CH_2Cl_2 (7 mL) under a nitrogen atmosphere. Stirring was continued for 17 h at –73 °C. Work up according to procedure B. Careful flash chromatography of the dark orange residue over silica gel, using Et_2O/*n*-pentane mixtures from 2–5% Et_2O, gave **6.36** (549.8 mg, 80%) as a clear colorless oil: $[\alpha]^{20}_{589}$ = +53.4 (c 0.058, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.71 (d, J = 16.0 Hz, 1 H), 7.55–7.51

(m, 2 H), 7.40–7.36 (m, 3 H), 6.47 (d, J = 16.0 Hz, 1 H), 5.85 (ddd, J = 6.3, 10.5, 17.0 Hz, 1 H), 5.36–5.27 (m, 2 H), 5.21 (td, J = 1.2, 10.6 Hz, 1 H), 1.82–1.65 (m, 2 H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.2 (s), 144.6 (d), 136.3(d), 134.4(s), 130.2 (d), 128.8 (d, 2 x C), 127.9(d, 2 x C), 118.3 (d), 116.7 (t), 76.0 (d), 27.3 (t), 9.4 (q); exact mass m/z calcd for $C_{14}H_{16}O_2$ 216.1150, found 216.1160; HPLC analysis indicated an enantiomeric excess of at least 98 % [Chiralcel OB-H column; flow: 0.5 mL/min; *n*-heptane/*i*-PrOH: 99.5:0.5; λ = 225 nm; major enantiomer (+)-**6.36**, t_R = 16.83 min; minor enantiomer, racemate, (–)-**6.36**, t_R = 17.8 min]. The absolute stereochemistry based on the conversion to known **6.40**.[43]



(E)-3-Phenyl-acrylic acid (S)-1-vinyl-pentyl ester: **6.43**.

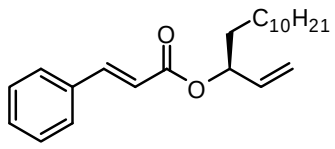
Butylmagnesium bromide (3.0 M, 0.75 mL, 2.25 mmol) was added dropwise over 5 min to a stirred and cooled (–69 °C) solution of **6.26** (305 mg, 1.14 mmol), CuBr•SMe_2 (6.7 mg, 32.6 µmol) and (R,R_{fc})-TaniaPhos (31.4 mg, 45.7 µmol) in CH_2Cl_2 (4 mL) under a nitrogen atmosphere. Stirring was continued for 21 h at –69 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–4% Et_2O, gave **6.43** (259 mg, 92%) as a clear colorless oil: $[\alpha]^{20}_{589}$ = +32.6 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.71 (d, *J* = 16.0 Hz, 1 H), 7.50–7.49 (m, 2 H), 7.40–7.34 (m, 3 H), 6.46 (d, *J* = 16.0 Hz, 1 H), 5.85 (ddd, *J* = 6.3, 10.5, 17.2 Hz, 1 H), 5.42–5.35 (m, 1 H), 5.29 (td, *J* = 1.3, 17.3 Hz, 1 H), 5.19 (td, *J* = 1.3, 10.5 Hz, 1 H), 1.76–1.60 (m, 2 H), 1.45–1.25 (m, 4H), 0.91 (broad t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.1 (s), 144.6 (d), 136.6 (d), 134.4 (s), 130.1 (d), 128.8 (d, 2 x C), 128.0 (d, 2 x C), 118.3 (d), 116.4 (t), 74.8 (d), 33.9 (t), 27.2 (t), 22.4 (t), 13.9 (q); exact mass m/z calcd for $C_{16}H_{20}O_2$, 244.1463 found; 244.1469, found; A trace amount of the S_N2-product was detected by ^{1}H NMR spectroscopy. The absolute stereochemistry and enantioselectivity were determined by the conversion to known **6.55** and comparison of reported optical rotation.[44]



(+)-(E)-3-Phenyl-acrylic acid (S)-1-vinyl-hexyl ester: **6.44**.

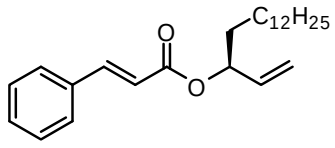
Pentylmagnesium bromide (2.0 M, 1.13 mL, 2.26 mmol) was added dropwise over 5 min to a stirred and cooled (–69 °C) solution of **6.26** (301.0 mg, 1.126 mmol), CuBr•SMe_2 (6.8 mg, 33.1 µmol) and (R,R_{fc})-TaniaPhos (30.8 mg, 44.8 µmol) in CH_2Cl_2 (4 mL) under a nitrogen atmosphere. Stirring was continued for 20 h at –69 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–4% Et_2O, gave **6.44** (244.0 mg, 84%) as a clear colorless oil: $[\alpha]^{20}_{589}$ = +31.1 (*c* 0.26, $CHCl_3$); ^{1}H NMR (400 MHz) δ7.69 (d, *J* = 16.0 Hz, 1 H), 7.56–7.51 (m, 2 H), 7.41–7.36 (m, 3 H), 6.46 (d, *J* = 16.0 Hz, 1 H), 5.85 (ddd, *J* = 6.3, 10.5, 16.9 Hz, 1 H), 5.41–5.34 (m, 1 H), 5.29 (td, *J* = 1.3, 17.2 Hz, 1 H), 5.19 (td, *J* = 1.3, 10.5 Hz, 1 H), 1.80–1.60 (m, 2 H), 1.45–1.25 (m, 6 H), 0.86 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz)

δ166.3 (s), 144.7 (d), 136.7 (d), 134.5 (s), 130.2 (d), 128.8 (d, 2 x C), 128.0 (d, 2 x C), 118.4 (d), 116.5 (t), 74.7 (d), 34.2 (t), 31.6 (t), 24.7 (t), 22.5 (t), 14.0 (q); exact mass m/z calcd for $C_{17}H_{22}O_2$, 258.1620 found; 258.1606. The absolute stereochemistry and enantioselectivity were determined by the conversion to known **6.55**. [45]



(+)-(E)-3-Phenyl-acrylic acid (S)-1-vinyl-dodecyl ester: **6.45**.

Undecanemagnesium bromide (2.0 M, 1.1 mL, 2.2 mmol) was added dropwise over 5 min to a stirred and cooled (–57 °C) solution of **6.26** (301.4 mg, 1.128 mmol), CuBr•SMe_2 (6.7 mg, 32.6 µmol) and (*R*,R_{fc})-TaniaPhos (31.4 mg, 45.7 µmol) in CH_2Cl_2 (4 mL) under a nitrogen atmosphere. Stirring was continued for 17 h at –68 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–2% Et_2O, gave impure **6.46** (contaminated with homo-coupled Grignard reagent). A second careful column chromatography purification over silica gel, using Et_2O/*n*-pentane mixtures from 0–2% Et_2O/*n*-pentane gave pure **6.45** as a clear colorless oil (279.0 mg, 73%): $[\alpha]^{20}_{589}$ = +16.9 (*c* 0.22, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.71 (d, *J* = 16.0 Hz, 1 H), 7.56–7.49 (m, 2 H), 7.42–7.34 (m, 3 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 5.86 (ddd, *J* = 6.3, 10.5, 16.9 Hz, 1 H), 5.43–5.35 (m, 1 H), 5.30 (apparent d, *J* = 17.2 Hz, 1 H), 5.20 (apparent d, *J* = 10.5 Hz, 1 H), 1.80–1.60 (m, 2 H), 1.45–1.15 (m, 18H), 0.89 (broad t, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.2 (s), 144.9 (d), 136.6 (d), 134.4 (s), 130.1 (d), 128.8 (d, 2 x C), 128.0 (d, 2 x C), 118.4 (d), 116.4 (t), 74.8 (d), 34.3 (t), 31.9 (t), 29.6 (t), 29.6 (t), 29.5 (t), 29.5 (t), 29.3 (t), 29.3 (t), 25.0 (t), 22.6 (t), 14.1 (q); exact mass m/z calcd for $C_{23}H_{34}O_2$ 342.2559, found 342.2563. The absolute stereochemistry and enantioselectivity were determined by the conversion to known **6.56**

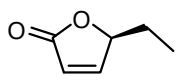


(+)-(E)-3-Phenyl-acrylic acid (S)-1-vinyl-tetradecyl ester: **6.46**.

Tridecanemagnesium bromide (0.**7** M, 4.0 mL, 2.8 mmol) was added dropwise over 5 min to a stirred and cooled (–55 °C) solution of **6.26** (300.0 mg, 1.123 mmol), CuBr•SMe_2 (6.7 mg, 32.6 µmol) and (*R*,R_{fc})-TaniaPhos (30.4 mg, 44.2 µmol) in CH_2Cl_2 (4 mL) under a nitrogen atmosphere. Stirring was continued for 21 h at –55 °C. Work up according to procedure B. Flash chromatography of the dark orange residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–1% Et_2O, gave impure **6.46** (contaminated with homo-coupled Grignard reagent). A second careful column using Et_2O/*n*-pentane mixtures from 0–2% Et_2O, gave **6.46** as a clear colorless oil (281 mg, 68%): $[\alpha]^{20}_{589}$ = +12.9 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz) δ 7.71 (d, *J* = 16.0 Hz, 1 H), 7.56–7.48 (m, 2 H), 7.42–7.34 (m, 3 H), 6.47 (d, *J* = 16.0 Hz, 1 H), 5.86 (ddd, *J* = 6.3, 10.5, 17.2 Hz, 1 H), 5.44–5.35 (m, 1 H), 5.30 (td, *J* = 1.4, 17.3 Hz, 1 H), 5.19 (td, *J* = 1.6, 10.5 Hz, 1 H), 1.80–1.60 (m, 2 H), 1.45–1.15 (m, 20H), 0.90 (broad t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 166.1 (s), 144.5

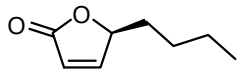
(d), 136.6 (d), 134.4 (s), 130.1 (d), 128.7 (d, 2 x C), 127.9 (d, 2 x C), 118.3 (d), 116.4 (t), 74.8 (d), 34.2 (t), 31.9 (t), 29.6 (t), 29.6 (t), 29.6 (t, 2 x C), 29.5 (t), 29.4 (t), 29.3 (t), 29.3 (t), 25.0 (t), 22.6 (t), 14.0 (q); exact mass m/z calcd for $C_{25}H_{38}O_2$ 370.2872, found 370.2856.

Synthesis of γ-butenolides



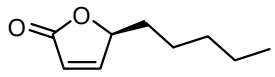
(+)-(S)-5-ethyl-2(5H)-furanone: **6.40**.[43]

Hoveyda-Grubbs 2nd generation (HG^{II}) catalyst[46] (15.3 mg, 0.024 mmol) was tipped into a stirred, dilute (0.005M) solution of **6.36** (55.2 mg, 0.255 mmol) in, degassed CH_2Cl_2 (50 mL) under a nitrogen atmosphere. The reaction flask was placed in a preheated oil bath (60 °C) and stirred while heating to reflux for 43 h. The reaction mixture was cooled to room temperature and the solvent carefully removed under vacuum. Flash chromatography of the residue over silica gel, using EtOAc/*n*-pentane mixtures from 10–50% EtOAc, gave **6.40** (21.8 mg, 78%) as a volatile colorless oil: $[\alpha]^{29}_{589}$ = + 76.9 (*c* 0.026, $CHCl_3$); Lit[43] $[\alpha]^{22}_{589}$ = + 105 (*c* 4.1, CH_2Cl_2); ^{1}H NMR (400 MHz) δ 7.44 (dd, *J* = 1.5, 5.7 Hz, 1 H), 6.10 (dd, *J* = 2.0, 5.7 Hz, 1 H), 4.99 (tdd, *J* = 1.8, 5.3, 1.8 Hz, 1 H), 1.90–168 (m, 2 H), 0.99 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.1 (s), 155.8 (d), 121.6 (d), 84.2 (d), 26.2 (t), 8.9 (q); HPLC analysis indicated an enantiomeric excess of 98% [Chiralcel OB-H column; flow: 0.5 mL/min; *n*-heptane/*i*-PrOH: 90:10; λ = 210 nm; major enantiomer (+)-**6.40**, t_R = 26.93 min; minor enantiomer (–)-**6.40**, t_R = 30.42 min].



(+)-(S)-5-butyl-2(5H)-furanone: **6.55**.[44]

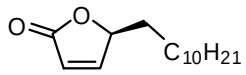
HG^{II} (7.5 mg, 0.012 mmol) was tipped into a stirred, dilute (4.6 mM) solution of **6.43** (169.0 mg, 0.692 mmol) in, degassed CH_2Cl_2 (150 mL) under a nitrogen atmosphere. The reaction flask was placed in a preheated oil bath (80 °C) and stirred while heating to reflux for 7 d (An additional amount HG^{II} catalyst (37.5 mg) was tipped in the solution during the course of the reaction in 5 portions of 7.5 mg). The reaction mixture was cooled to room temperature and the solvent removed under vacuum. Flash chromatography of the residue over silica gel, using Et_2O/*n*-pentane mixtures from 0/20% Et_2O, gave **6.55** (72 mg, 74%) as a colorless oil: $[\alpha]^{29}_{589}$ = +103.5 (*c* 0.026, $CHCl_3$), Lit[44] : $[\alpha]^{22}_{589}$ +100:4 (c 1.01, $CHCl_3$), +100.8 (c 1.0, $CHCl_3$, >98% ee (*S*)); ^{1}H NMR (400 MHz) δ 7.43 (dd, *J* = 5.7, 1.5 Hz, 1 H), 6.03 (dd, *J* = 5.7, 2.0 Hz, 1 H), 5.02-4.96 (m, 1 H), 1.81-1.53 (m, 2 H), 1.45-1.24 (m, 4 H), 0.85 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.0 (s), 156.3 (d), 121.2 (d), 83.3 (d), 32.7 (t), 26.9 (t), 22.2 (t), 13.6 (q); exact mass m/z calcd for $C_8H_{12}O_2$ 140.0837, found 140.0835;



(*+)-(S)-5-pentyl-2(5H)-furanone*: **6.56**.[44,45]

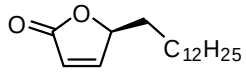
HG^{II} (7.5 mg, 0.012 mmol) was tipped into a stirred, dilute (0.005M) solution of **6.44** (197.8 mg, 0.75 mmol) in degassed CH_2Cl_2 (150 mL) under a nitrogen atmosphere. The reaction flask was placed in a preheated oil bath (60 °C) and stirred while heating to reflux for 7 d (An

additional amount HG^{II} (37.5 mg) was tipped in the solution during the course of the reaction in 5 portions of 7.5 mg). The reaction mixture was cooled to room temperature and the solvent carefully removed under vacuum. Flash chromatography of the residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–20% Et_2O, gave **6.56** (83 mg, 72%) as a colorless oil: $[\alpha]^{29}_{589}$ = + 94.0 (*c* 0.3, $CHCl_3$); ^1H NMR (400 MHz) δ 7.44 (dd, *J* = 5.7, 1.5 Hz, 1 H), 6.08 (dd, *J* = 5.7, 2.0 Hz, 1 H), 5.02 (tdd, *J* = 7.3, 5.3, 1.7 Hz, 1 H), 1.80-1.57 (m, 2 H), 1.49-1.21 (m, 6 H), 0.87 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.1 (s), 156.3 (d), 121.3 (d), 83.3 (d), 33.0 (t), 31.3 (t), 24.5 (t), 22.3 (t), 13.8 (q); exact mass m/z calcd for $C_9H_{14}O_2$ 154.0994, found 154.0987. The absolute configuration and enantioselectivity were correlated to lit[45]: $[\alpha]^{22}_{589}$ +89.9 (c 1.85, $CHCl_3$, 95% ee), $CHCl_3$), $[\alpha]^{25}_{589}$ +89.53 (c 1.36, $CHCl_3$, >99% ee (*S*)).



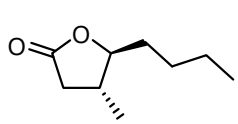
(+)-(S)-5-undecyl-2(5H)-furanone: **6.57**. [28f]

HG^{II} (7.5 mg, 0.012 mmol) was tipped into a stirred, dilute (0.005M) solution of **6.45** (279 mg, 0.81 mmol) in degassed CH_2Cl_2 (150 mL) under a nitrogen atmosphere. The reaction flask was placed in a preheated oil bath (60 °C) and stirred while heating to reflux for 14 d (an additional amount HG^{II} (37.5 mg) was tipped in the solution during the course of the reaction in 5 portions of 7.5 mg). The reaction mixture was cooled to room temperature and the solvent carefully removed under vacuum. Flash chromatography of the residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–20% Et_2O, gave **6.57** (138.5 mg, 71%) as a white waxy solid: $[\alpha]^{23}_{589}$ = +91.5 (*c* 0.78, $CHCl_3$); ^1H NMR (400 MHz) δ 7.43 (dd, *J* = 5.7, 0.8 Hz, 1 H), 6.05 (dd, *J* = 5.6, 1.7 Hz, 1 H), 4.99 (tdd, *J* = 9.1, 5.2, 1.75 Hz, 1 H), 1.80-1.54 (m, 2 H), 1.46-1.12 (m, 18 H), 0.83 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.0 (s), 156.3 (d), 121.2 (d), 83.3 (d), 33.0 (t), 31.7 (t), 29.4 (t, 2 x C), 29.3 (t), 29.2 (t), 29.1 (t), 29.1 (t), 24.8 (t), 22.5 (t), 13.9 (q). The absolute configuration and ee were correlated to lit[28e]: $[\alpha]^{22}_{589}$ –66.6 (c 1.945, $CHCl_3$, 98% ee).



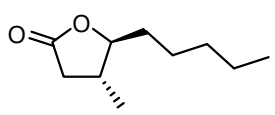
(+)-(S)-5-tridecyl-2(5H)-furanone: **6.58**. [28f]

HG^{II} (7.5 mg, 0.012 mmol) was tipped into a stirred, dilute (0.005M) solution of **6.46** (271 mg, 0.73 mmol) in degassed CH_2Cl_2 (150 mL) under a nitrogen atmosphere. The reaction flask was placed in a preheated oil bath (60 °C) and stirred while heating to reflux for 14 d (an additional amount HG^{II} (37.5 mg) was tipped in the solution during the course of the reaction in 5 portions of 7.5 mg). The reaction mixture was cooled to room temperature and the solvent carefully removed under vacuum. Flash chromatography of the residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–15% Et_2O, gave **6.58** (130.2 mg, 67%) as a white waxy solid: ^1H NMR ($CDCl_3$, 400 MHz) δ 7.44 (dd, *J* = 5.7, 1.4 Hz, 1 H), 6.07 (dd, *J* = 5.7, 2.0 Hz, 1 H), 5.04-4.98 (m, 1 H), 1.82-1.56 (m, 2 H), 1.47-1.19 (m, 22 H), 0.85 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 173.0 (s), 156.2 (d), 121.3 (d), 83.3 (d), 33.1 (t), 31.8 (t), 29.5 (t), 29.5 (t, 2 x C), 29.5 (t), 29.4 (t), 29.2 (t), 29.2 (t), 29.2 (t), 24.8 (t), 22.5 (t), 14.0 (q).



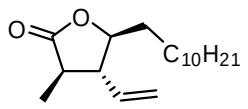
(–)-(4R,5S)-4-Methyl-5-butyl-dihydro-furan-2-one: (–)-whiskey lactone **6.59**.[28e,f]

6.57 (33.7 mg, 0.24 mmol) in Et_2O (1.5 ml) was added to a suspension of CuI (240.7 mg, 1.26 mmol) and MeLi (1.6 ml, 2.6 mmol, 1.6M in hexanes) in Et_2O (1 ml) at –20 °C and stirred for 1 h. The mixture was quenched with sat. aq. NH_4Cl and filtered over a small plug of cotton wool and sand. The sand was washed with Et_2O and the filtrate was partitioned between H_2O and Et_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* yielding a waxy solid. Flash chromatography of the residue over silica gel, using Et_2O/*n*-pentane mixtures from 10–30% Et_2O, gave **6.59** (31 mg, 83%) as a white waxy solid: $[\alpha]^{20}_{589}$ = –83.3 (*c* 0.17, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 3.98 (dt, *J* = 8.15, 8.12, 4.03 Hz, 1 H), 2.83-2.54 (m, 1 H), 2.25-2.08 (m, 2 H), 1.74-1.24 (m, 6 H), 1.11 (d, *J* = 6.44 Hz, 3 H), 0.89 (t, *J* = 7.18 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 176.5 (s), 87.4 (d), 37.1 (t), 36.0 (d) , 33.6 (t), 27.8 (t), 22.4 (t), 17.4 (q), 13.8 (q).



(–)-(4R,5S)-4-Methyl-5-pentyl-dihydro-furan-2-one: (–)-cognac lactone **6.60**.[28e,f]

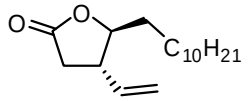
6.58 (34 mg, 0.22 mmol) in Et_2O (1.5 ml) was added to a suspension of CuI (242 mg, 1.30 mmol) and MeLi (1.62 ml, 2.6 mmol, 1.6M, hexanes) in Et_2O (1 ml) at –35 °C. The mixture was slowly warmed to –10 °C and stirred for 2 h. The mixture was partitioned between sat. aq. NH_4Cl and Et_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent removed *in vacuo*. Flash chromatography of the residue over silica gel, using Et_2O/*n*-pentane mixtures from 10–20% Et_2O, gave **6.60** (36 mg, 96%) as a white waxy solid: $[\alpha]^{20}_{589}$ = –73.4 (*c* 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz); δ 3.99 (dt, *J* = 8.0, 7.8, 4.0 Hz, 1 H), 2.72-2.69 (m, 1 H), 2.24-2.14 (m, 2 H), 1.72-1.26 (m, 8 H), 1.12 (d, *J* = 6.4 Hz, 3 H), 0.88 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 176.5 (s), 87.4 (d), 37.1 (t), 36.0 (d), 33.9 (t), 31.5 (t), 25.3 (t), 22.4 (t), 17.4 (q), 13.9 (q).



(3R,4R,5S)-3-Methyl-5-undecyl-4-vinyl-dihydro-furan-2-one: **6.65**.

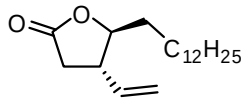
6.66 (14.7 mg, 0.056 mmol) in THF (1.5 ml) was added to $LiN(SiMe_3)_2$ (0.24 ml, 0.06 mmol, 0.25M THF) at –70 °C. Stirring was continued for 20 min before MeI (0.034 ml, 0.56 mmol) was added at –78 °C and the reaction mixture was stirred for 16 h. Aq. HCl (2 ml, 2N) was added and the reaction mixture was removed from the cold bath. The reaction mixture was partitioned between Et_2O and water, and the aqueous layer extracted three times with Et_2O. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. Flash chromatography of the residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–30% Et_2O, gave a 1:1 mixture of diastereoisomers (^{1}H NMR). Subjection of the mixture, to equilibrating conditions (DBU/MeOH) for 18 h resulted in the exclusive formation of **6.65**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.72-5.60 (m, 1 H), 5.24-5.18 (m, 2 H), 4.12-4.00 (m, 1 H), 2.50-2.38 (m, 1 H), 2.34-2.24 (m,

1 H), 1.80-1.22 (m, 20 H), 1.20 (d, *J* = 6.96 Hz, 3 H), 0.88 (t, *J* = 6.84, 6.84 Hz, 3 H); ^{13}C NMR spectroscopy showed the presence of an impurity that proved difficult to remove from **6.66** by washing with aq. HCl (2 N) or flash column chromatography.



(–)-(4S,5S)-5-Undecyl-4-vinyl-dihydro-furan-2-one: **6.66**.

6.57 (27.0 mg, 0.11 mmol) in Et_2O (2 ml) was added to a stirred suspension (dark purple) of CuI (105 mg, 0.55 mmol) and vinyllithium (2.26 ml, 1.1 mmol, 0.48M in *n*-pentane/Et_2O) at –30 °C and stirring was continued for 30 min before quenching with sat. aq. NH_4Cl. The reaction mixture was removed from the cooling bath and filtered over a small plug of cotton wool and sand (wash 2 x CH_2Cl_2) before partitioning between CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated *in vacuo*. Flash chromatography of the residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–10% Et_2O, gave *trans*-(–)-**6.66** (27.3 mg**,** 92%) as a waxy solid: $[\alpha]^{29}_{589}$ = –52.3 (*c* 0.34, $CHCl_3$) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.71 (ddd, *J* = 17.8, 10.1, 7.8 Hz, 1 H), 5.20-5.12 (m, 2 H), 4.13 (dt, *J* = 8.4, 3.8 Hz, 1 H), 2.88-2.59 (m, 2 H), 2.43 (dd, *J* = 17.1, 10.4 Hz, 1 H), 1.79-1.05 (m, 20 H), 0.87 (t, *J* = 6.8, 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.7 (s), 135.7 (d), 117.9 (t), 84.8 (d), 46.3 (d), 35.4 (t), 33.6 (t), 31.8 (t), 29.5 (t), 29.5 (t, 2 x C), 29.4 (t), 29.3 (t, 2 x C), 25.7 (t), 22.6 (t), 14.0 (q); exact mass m/z calcd for $C_{17}H_{30}O_2$ 266.2237, found 266.2246.



(–)-(4S,5S)-5-tridecyl-4-vinyl-dihydro-furan-2-one: **6.67**.

6.58 (30.0 mg, 0.11 mmol) in Et_2O (1.5 ml) was added to a stirred suspension (dark purple) of CuI (106 mg, 0.56 mmol) and vinyl lithium (2.0 ml, 1.13 mmol, 0.56M in *n*-pentane/ Et_2O) at –33 °C and stirring was continued for 30 min before quenching with sat. aq. NH_4Cl. The reaction mixture was removed from the cooling bath and filtered over a small plug of cotton wool and sand (wash 2 x CH_2Cl_2) before partitioning between CH_2Cl_2 and water. The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. Flash chromatography of the residue over silica gel, using Et_2O/*n*-pentane mixtures from 0–10% Et_2O, gave *trans*-(+)-**6.67** (21.2 mg**,** 66%) as a white crystalline solid: Mp.: 45-46 °C; $[\alpha]^{29}_{589}$ = –62.5 (*c* 0.08, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.69 (ddd, *J* = 17.1, 10.2, 7.9 Hz, 1 H), 5.18-5.10 (m, 2 H), 4.10 (dt, *J* = 8.4, 3.7 Hz, 1 H), 2.82-2.59 (m, 2 H), 2.41 (dd, *J* = 17.1, 10.5 Hz, 1 H), 1.77-1.11 (m, 24 H), 0.84 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 175.8 (s), 135.7 (d), 118.0 (t), 84.8 (d), 46.3 (d), 35.4 (t), 33.6 (t), 31.9 (t), 29.6 (t), 29.6 (t, 2 x C), 29.6 (t), 29.5 (t), 29.4 (t), 29.3 (t), 29.3 (t), 25.7 (t), 22.6 (t), 14.1 (q); exact mass m/z calcd for $C_{19}H_{34}O_2$ 294.2559, found 294.2561.

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